§ 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

Please amend the application as follows:

In the Claims:

Please cancel claims 1-47.

Please add the following new claims:

---

48. (New) A method of generating a hybrid mammalian cell comprising:

(a) preparing a cytoplast fragment from a mammalian oocyte or fertilized zygote (the cytoplast donor);

(b) preparing a cell with a donor nucleus or a karyoplast with a donor nucleus (nuclear donor) which is taken from any mammalian species; and

(c) fusing said cytoplast fragment with said cell or said karyoplast,

thereby producing a hybrid mammalian cell.

49. (New) The method of claim 48, wherein said cytoplast fragment is produced by vortexing said mammalian oocyte or fertilized zygote.

50. (New) The method of claim 48, wherein the zona pellucida of said mammalian oocyte or fertilized zygote is removed.

51. (New) The method of claim 50, wherein said zona pellucida is removed by (a) treatment with an enzyme or an acidified Tyrodes solution, (b) micromanipulation followed by treatment with a microfilament inhibitor and vortexing, or (c) micropipeting in the presence of an microfilament inhibitor with mechanical aspiration of cytoplasm.

52. (New) The method of claim 51, wherein said enzyme is Pronase.

B1 cont

53. (New) The method of claim 51, wherein said microfilament inhibitor is cytochalasin B.

54. (New) The method of claim 48, wherein said mammalian oocyte or fertilized zygote is enucleated.

55. (New) The method of claim 54, wherein said mammalian oocyte or fertilized zygote is enucleated by micromanipulation or centrifugation in an appropriate gradient in the presence of a microfilament inhibitor.

56. (New) The method of claim 48, wherein said mammalian oocyte is matured *in vivo*.

57. (New) The method of claim 48, wherein said mammalian oocyte is matured *in vitro*.

58. (New) The method of claim 48, wherein said mammalian oocyte is selected from the group consisting of: an activated, low MPF oocyte; an aged, unactivated, low MPF oocyte; and an unactivated, high MPF, metaphase II oocyte.

59. (New) The method of claim 58, wherein said mammalian oocyte is an unactivated, high MPF, metaphase II oocyte.

B1 Cont

60. (New) The method of claim 48, wherein said cytoplast donor is from a different species from that of the nuclear donor.

61. (New) The method of claim 48, wherein said cytoplast donor is from the same species as that of the nuclear donor.

62. (New) The method of claim 48, wherein said cytoplast donor is derived from a non-human mammalian species.

63. (New) The method of claim 62, wherein said cytoplast donor is derived from mouse, rat, rabbit, sheep goat, pig, or cow.

64. (New) The method of claim 63, wherein said cytoplast donor is derived from cow.

65. (New) The method of claim 48, wherein said nuclear donor is derived from fibroblasts, granulosa cells, cumulus cells, oviductal epithelium, mammary gland cells, fetal fibroblasts, keratinocytes, hepatocytes, respiratory epithelial cells, neuronal cells, C43+ stem cells, granulocytes, or mononuclear peripheral blood cells.

66. (New) The method of claim 48, wherein said nuclear donor cell is a karyoplast.

B1 cont

67. (New) The method of claim 66, wherein said karyoplast is an interphase cell.

68. (New) The method of claim 66, wherein said karyoplast is cytoplasm deficient.

69. (New) The method of claim 66,wherein said karyoplast is enriched with mitochonria.

70. (New) The method of claim 48, wherein said fusing of said cytoplast fragment with said nuclear donor is mediated by electrical fusion, chemical fusion, viruses, liposomes or cell surface proteins.

71. (New) The method of claim 70, wherein said fusing is mediated by electrical fusion.

72. (New) The method of claim 70, wherein said fusing is mediated by polyethylene glycol or high pH-low osmolarity.

73. (New) The method of claim 48, further comprising an activation step.

74. (New) The method of claim 73, wherein said activation occurs before said fusion step.

B1 cont

75. (New) The method of claim 73, wherein said activation occurs after said fusion step.

76. (New) The method of claim 73, wherein said activation is meditated by electrical pulse, ionomycon/DMAP, cytochalasin/cyclohexamide, strontium, adenophostin, disintegin RGD peptide, DDT/thimerosal, or sperm factor.

77. (New) The method of claim 48, wherein said donor nucleus is from an embryonic, fetal, or adult cell/karyoplast.

78. (New) The method of claim 48, wherein said donor nucleus is from a diploid cell.

79. (New) The method of claim 78, wherein said donor nucleus is from a cell or karyoplast synchronized in G0/G1; or by a cell or karyoplast arrested at the G1/S border.

80. (New) The method of claim 48, wherein said donor nucleus is matched to the cell cycle stage of the cytoplast donor.

81. (New) The method of claim 48, wherein said donor nucleus is from a differentiated or undifferentiated stem cell, or differentiated or undifferentiated somatic cell.

B1 Cont'd

82. (New) The method of claim 48, wherein said donor nucleus is from a human, cow, bull, pig, sheep, goat, camel, waterbuffalo, primate, rodent or lagomorph.

83. (New) The method of claim 48, wherein said donor nucleus is from a human.

84. (New) The method of claim 48, wherein the donor nucleus has been genetically modified.

85. (New) The method of claim 84, wherein said donor nucleus is genetically modified with a gene designed to correct a genetic defect or supply cells with a capacity to produce a protein, enzyme, enzyme product, cellular component or a therapeutic agent.

86. (New) The method of claim 48, wherein the mitochondria of the donor cytoplast is made replication incompetent.

87. (New) The method of claim 86, wherein said donor cytoplast contains congenital mitochondrial lesions.

88. (New) The method of claim 86, wherein said donor cytoplast or cytoplast fragment is incubated with an inhibitor of mitochondrial DNA replication.

89. (New) The method of claim 86, wherein said donor cytoplast or cytoplast fragment is incubated with EtBr.

(B) Cont

90. (New) The method of claim 48, wherein the hybrid cell is supplemented with mitochondria derived from the same species as the nuclear donor.

91. (New) The method of claim 90, wherein mitochondria is derived from the same animal or individual as the nuclear donor.

92. (New) The method of claim 90, wherein said mitochondria supplementation is mediated by fusion of an enucleated cytoplast with the hybrid cell.

93. (New) The method of claim 92, wherein said enucleated cytoplast is derived from platelets.

94. (New) The method of claim 48, wherein said nuclear donor cell is stably transfected with a gene encoding a mitochondrial maintenance factor.

95. (New) The method of claim 94, wherein said gene is mtTFA.

96. (New) The method of claim 48, wherein said donor cell is transiently transfected with a gene encoding a modulator of histone acetylation or a modulator of chromatin structure.

97. (New) The method of claim 96, wherein said gene is histone deacetylase.

(B) cont'd

98. (New) The method of claim 48, further comprising the step of establishing a population of hybrid cells derived from said hybrid cell.

99. (New) A hybrid cell generated by the method of claim 48.

100. (New) A population of hybrid cells generated by the method of claim 98.

101. (New) The method of claim 98, further comprising the step of culturing the hybrid cell population in the presence of compounds or factors which induce gene transcription, thereby producing an activated hybrid cell population.

102. (New) The method of claim 101, wherein said compounds or factors is a reversible inhibitor of histone deacetylase.

103. (New) The method of claim 102, wherein said reversible inhibitor of histone deacetylase is butyrate.

104. (New) The method of claim 102, wherein said reversible inhibitor of histone deacetylase is trichostatin A.

105. (New) The method of claim 101, further comprising the step of culturing the activated hybrid cell population in a medium that maintains the dedifferentiated state of the activated hybrid cell population and support the development and proliferation of the activated hybrid cell population.

B1 Cont

106. (New) The method of claim 105, wherein said medium comprises cytokines, LIF, steel factor, or CGT44.

107. (New) The method of claim 105, wherein said medium comprises a feeder layer of mitotically inactivated primary fibroblast cells.

108. (New) The method of claim 105, further comprising the step of removing activated hybrid cell population from said medium and culturing said activated hybrid cell population in a second medium which induces differentiation of embryonic stem cells.

109. (New) The method of claim 108, wherein said second medium comprises a factor which induces neural pathway differentiation.

110. (New) The method of claim 109, wherein said factor is retinoic acid, fibroblast growth factor 2(FGF2), epidermal growth factor (EGF), or platelet-derived growth factor (PGDF).

111. (New) The method of claim 108, wherein said second medium comprises c-kit and erythropoietin.

112. (New) The method of claim 108, wherein said second medium comprises macrophage colony stimulating factor (M-CSF), intereleukin 1 and interleukin 3.

B1 Cont

113. (New) The method of claim 108, wherein said second medium comprises retinoic acid, insulin, and tri-iodothyronine.

114. (New) The method of claim 108, wherein said second medium comprises retinoic acid and dibutryl cyclic AMP.

115. (New) The method of claim 108, wherein said second medium comprises cells from the pancreatic bud.

116. (New) The method of claim 98, further comprising the step of transfecting cells of the hybrid cell population with genes encoding activators or transcription factors.

117. (New) The method of claim 98, wherein said cells are transfected with Myo D, PPAR gamma, or C/EBP alpha.

118. (New) A method of generating and enriching a population of hybrid cells comprising:

(a) preparing a population of cytoplasts fragments stained with a first color;

(b) preparing a population of nuclear donor cells transfected with a gene that encodes a fluorescent protein, which is capable of fluorescing a second color;

(c) fusing said population of cytoplast fragments and said population of nuclear donor cells, thereby producing a population of products comprising fused products, unfused cytoplast fragments, and unfused nuclear donors, wherein said fused products comprise hybrid cells with a normal karyotype and aneuploidy cells;

(d) sorting the population of products by selecting for fused products and unfused cytoplasts marked by the first color; and

(e) further sorting the fused products by selecting for cells with a normal karyotype and marked by the second color.

119. (New) A method of generating and enriching a population of hybrid cells comprising:

(a) preparing a population of stained cytoplasts stained with a first color;

(b) preparing a population of nuclear donor cells, wherein the DNA of said nuclear donor cell is stained with a second color;

(c) fusing said population of cytoplasts and said population of nuclear donor cells, thereby producing a population of products comprising fused products, unfused cytoplasts, and unfused nuclear donors, wherein said fused products comprise hybrid cells with a normal karyotype and aneuploidy cells;

B1 Cont

(d) sorting the population of products by selecting for fused products and unfused cytoplasts marked by the first color; and

(e) further sorting the fused products by selecting for cells with a normal karyotype marked by the second color.